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(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No.

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(54) Title  
MICROSPHERES

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(71) Applicant(s)  
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(74) Attorney or Agent  
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(57) Claim

1. A method of continuously providing an active ingredient to a place where its presence is desired by means of a controlled release mechanism, the active ingredient being encapsulated in polymer particles which comprise part of an aqueous dispersion of such particles prepared by the steps of

- (a) dissolving in a polymer precursor at least one active ingredient which is completely soluble in the precursor to form a solution;
- (b) stably dispersing the solution in water in the presence of at least one colloid stabilising agent; and
- (c) converting the polymer precursor to polymer and thus forming a dispersion of controlled release microspheres;

the active ingredient being present at a level in

609571

Case No: AUS.1395

FORM I

Regulation 9

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

APPLICATION FOR A PATENT

We, ICI AUSTRALIA OPERATIONS PROPRIETARY LIMITED, of 1  
Nicholson Street, Melbourne, Victoria 3001, Australia, hereby  
apply for the grant of a Patent for an invention entitled:

"MICROSPHERES"

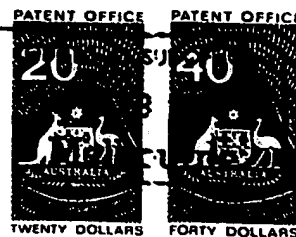
which is described in the accompanying Provisional  
Specification.

Our address for service is: C/- Industrial Property  
Section, ICI Australia Limited, 1 Nicholson Street, Melbourne,  
Victoria 3001, Australia.

LODGED AT SUB-OFFICE

25 FEB 1988

Melbourne



DATED this 25th day of February 1988

ALL AMENDMENTS ACCEPTED AND AMENDMENTS

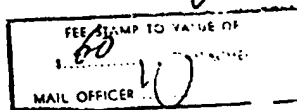
MAILED

6.2.91

ICI AUSTRALIA OPERATIONS  
PROPRIETARY LIMITED  
By its Duly Authorised Officer

J.R. Davy

TO: The Commissioner of Patents



Our Ref: AHS 100

FORM 7

COMMONWEALTH OF AUSTRALIA

Regulation 12(1)

Patents Act 1952 - 1969

DECLARATION IN SUPPORT OF AN APPLICATION FOR A PATENT

In support of an application made by ICI AUSTRALIA  
OPERATIONS PROPRIETARY LIMITED for a patent for an invention  
entitled: "MICROSPHERES"

I, E Ann Hull of ICI House, 1 Nicholson Street, Melbourne 3001  
do solemnly and sincerely declare that I am authorised by Australia  
ICI AUSTRALIA OPERATIONS PROPRIETARY LIMITED, the applicant  
for the patent to make this declaration on its behalf.

1. ICI AUSTRALIA OPERATIONS PROPRIETARY LIMITED is in  
possession of the invention, the subject of the  
application.
2. Matt TRAU of 492 Station Street, North Carlton 3054, Victoria, Australia

are the actual inventors of the invention and the facts  
upon which ICI AUSTRALIA OPERATIONS PROPRIETARY LIMITED  
is entitled to make the application are as follows:

The said ICI AUSTRALIA OPERATIONS PROPRIETARY LIMITED  
is the assignee of the said actual inventors.

DATED at

this 21 day of January, 1987

ICI AUSTRALIA OPERATIONS  
PROPRIETARY LIMITED  
By Its Duly Authorised Officer

... E Ann Hull ...

E Ann Hull

(11) AU-B-28951/89  
(10) 609571

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excess of the critical blooming concentration and the combination of microsphere size and colloid stabilising agent being such that the dispersion remains stable.



PATENTS ACT 1952-1973

Form 10

# COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Class:

Int. Cl:

609571

Application Number:

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Complete Specification—Lodged:

Accepted:

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Related Art:

## TO BE COMPLETED BY APPLICANT

Name of Applicant: ICI AUSTRALIA OPERATION PROPRIETARY LIMITED

Address of Applicant: 1 Nicholson Street  
Melbourne 3001, Victoria Australia

This document contains the  
amendments made under  
Section 49 and is correct for  
printing

Actual Inventor: Matt TRAU

1006220 31/01/39

Address for Service: Industrial Property Section  
ICI Australia Operations Proprietary Limited  
1 Nicholson Street  
P.O. Box 4311  
Melbourne 3001, Victoria Australia

Complete Specification for the invention entitled:  
"MICROSPHERES"

The following statement is a full description of this invention, including the best method of performing it known to me:—

\*Note: The description is to be typed in double spacing, pica type face, in an area not exceeding 250 mm in depth and 180 mm in width, on tough white paper of good quality and it is to be inserted inside this form.

- 1 -

## MICROSPHERES

This invention relates to controlled release microspheres and more particularly to controlled release microspheres for spraying applications.

5        There has recently been an upsurge in interest in controlled release microspheres, that is, polymer microspheres comprising encapsulated active ingredient which is released slowly into the environment surrounding the microspheres. The  
10        microspheres containing the active ingredient are commonly dried for storage and transport and redispersed in water for spraying. The active ingredient may be, for example, a herbicide or a  
15        pesticide, and the benefits of the encapsulation and subsequent controlled release include the prolonged effectiveness of the active ingredient.

Frequently, however, the quantity of active ingredient made available is insufficient to achieve an initial desirable state of affairs which can then be easily maintained by further release. For example, a crop suffering from a large growth of weeds may need a large initial dose of herbicide to kill off the weeds. The logical response to this problem would appear to be simply to increase the level of active ingredient. However, when this is done, there often arises the problem of "blooming", or the tendency of the active ingredient to migrate to the surface of the dried microspheres to form a layer there. The reasons for the occurrence of blooming are not completely understood, but one of them is believed to be the extent of solubility or compatibility of the active ingredient with the microsphere polymer. Blooming brings disadvantages such as the lowering of the concentration of active ingredient with resultant reduction of effectiveness, plus handling hazards as a result of the dust of the often highly toxic active ingredients formed on the surface.

The only known way of preventing blooming, one which is followed throughout the industry, is to keep the concentration of active ingredient below the concentration at which blooming will occur or to store at an elevated temperature (about 30°-40°C). There is for each combination of active ingredient and polymer a critical concentration (hereinafter referred to as "CBC") below which blooming will occur to a negligible extent. The CBC will vary according to the temperature and in order to avoid temperature - induced blooming, active ingredient concentrations are kept low. Such low concentrations naturally reduce the effectiveness of controlled release preparations.



There has now been found a method of using controlled release technology which method permits the delivery of a high concentration of active ingredient and in which blooming exerts a beneficial effect. There is therefore provided, according to the present invention, a method of continuously providing an active ingredient to a place where its presence is desired by means of a controlled release mechanism, the active ingredient being encapsulated in polymer particles which comprise part of an aqueous dispersion of such particles prepared by the steps of

- (a) dissolving in a polymer precursor at least one active ingredient which is completely soluble in the precursor to form a solution;
- (b) stably dispersing the solution in water in the presence of at least one colloid stabilising agent; and
- (c) converting the polymer precursor to polymer and thus forming a dispersion of controlled release microspheres;

the active ingredient being present at a level in excess of the critical blooming concentration and the combination of microsphere size and colloid stabilising agent being such that the dispersion remains stable.

There is further provided a liquid controlled release composition prepared as hereinabove described.

There is further provided a liquid controlled-release composition for use in a method of continuously providing an active ingredient as hereinabove described.

5 By "polymer precursor" is meant a liquid which can be converted into polymer microspheres. It may be, for example, a polymer dissolved in a solvent and dispersed in a continuous medium, the removal of which solvent brings about the formation  
10 of a dispersion of microspheres. It may be a liquid monomer or monomers within which polymerisation is initiated. The polymer used in this invention may be any polymer useful for the purposes of controlled release. In general, these  
15 polymers are thermoplastics of suitable solubility characteristics and typical examples of suitable polymers include ethylene-vinyl acetate copolymers; poly( -hydroxybutyrate -hydroxyvalerate) copolymers, polystyrene, poly( -caprolactone),  
20 poly(vinyl pyrrolidone), poly( -hydroxybutyrate) and polylactic and polyglycollic acids and copolymers.

It is permissible to include a filler in the polymer particles of the microspheres. Such fillers are inactive and may be used for several purposes.  
25 For example, a filler may be used to decrease the amount of polymer used in each microsphere, thereby decreasing the cost thereof. Alternatively, the filler particles may be used as a weight additive and to increase the density of the microspheres.  
30 This is useful where it is required that the microspheres do not float on or in a liquid, for example, in an agricultural application where it is required that the microspheres do not float away during irrigation. An example of a filler which may  
35 be used is bauxite tailings.

The active ingredient may be any suitable active ingredient known to the art provided that the active ingredient is completely soluble in the polymer precursor. It may be, for example, a herbicide, insecticide or a sunscreen composition. It is also possible that the active ingredient be an inorganic substance, such as a trace element; in this case, it is often necessary to complex the trace element to an organic molecule to ensure that the active ingredient is soluble in the polymer precursor. This may be useful in agricultural applications such as in the controlled release of trace elements into the soil. It is permissible to incorporate more than one active ingredient into a microsphere.

The concentration of active ingredient used is above the CBC. As previously mentioned, the CBC is different for each active ingredient/polymer combination, but it is readily determined by the person skilled in the art.

The solution of active ingredient in polymer precursor is stably dispersed in water in the presence of at least one colloid stabilising agent. By "colloid stabilising agent" is meant any chemical compound which is capable of stabilising a colloid. The colloid stabilising agent may be, for example, a well-known colloid stabiliser such as highly hydrolysed poly(vinyl acetate) (sometimes known as "polyvinyl alcohol") or it may be one of many types of nonionic surfactant.

In the first stage of the process according to the invention, the active ingredient is dissolved in the polymer precursor. As mentioned hereinabove, an unusually high quantity of active ingredient may be incorporated. If a filler is used it is added at

this stage. The filler may be surface treated to ensure that the particles disperse readily, or a dispersing agent may be added. This solution is then dispersed in water containing the colloid stabilising agent. The size of the droplets of solution and the quantity of colloid stabilising agent present should be such that the final dispersion of polymer microspheres is stable, that is, it does not settle appreciably on standing. This will be further discussed hereinafter.

Active ingredient-containing microspheres are formed from these droplets by converting the polymer precursor to polymer. This is done in any appropriate manner. For example, if the polymer precursor is a solution of a polymer in a liquid, the liquid is removed by, for example, evaporation. If the liquid is monomeric in nature, it may be converted to polymer by the addition of an initiator or a cross-linking agent.

The microspheres must be of such a size that they are stably dispersed. The factors governing the stability of the dispersion are the density of the microsphere material (including the active ingredient), the density of the aqueous phase, the size of the microspheres and the quantity of colloid stabilising agent present. As hereinabove mentioned, the size of the droplets of solution prior to polymer formation must be such that appropriately - sized microspheres will be obtained. The determination of all of these parameters and their use to attain a stable dispersion is well within the skill of the art. It has been found as a general rule that polymer microspheres in the size range of from 0.5 - 20  $\mu\text{m}$  give the best results.

The "size" in this case is the mean particle size in the distribution of sizes which inevitably results from a typical emulsification process. In the most preferred case, the overall size range of the particles lies between 0.5 and 20  $\mu$ m with the mean size as small as possible. The quantity of colloid stabilising agent required can readily be determined, but is typically from 1-5% by weight of the initial emulsion.

10        The result of the abovementioned process is a stable suspension of active ingredient-containing microspheres which can be applied directly in any suitable situation. The suspensions are storage - stable, requiring only a minimum of agitation to  
15        render them homogeneous, and active ingredient does not migrate to the microsphere surface or pass into the continuous phase to any appreciable extent. When the dispersion is applied and the continuous phase is removed, blooming occurs quickly in the  
20        highly active ingredient-laden microspheres. This contributes a large initial charge of active ingredient, the rest of the active ingredient being released more slowly over time. Such a suspension is very useful in, for example, a weed- or  
25        pest-infested crop wherein there can be a high initial "kill" followed by a slower release which maintains the weedless or pestless situation.

      The invention is further illustrated by the following examples in which all parts are expressed  
30        by weight.

#### Example 1

Preparation of a dispersion of controlled release ethylene-vinyl acetate (EVA) copolymer microspheres containing pesticide.

6.25 parts of an EVA copolymer (18% vinyl acetate content) and 3.13 parts of 'chlorpyrifos' (trademark) pesticide was dissolved in 368 parts of chlor form at 55°C. This mixture was then added to a stirred, heated (55°C) 2% w/w aqueous solution of an 88% hydrolysed grade of poly(vinyl acetate), a 4% w/w aqueous solution of which has a viscosity of 30 cps at 20°C ('Gohsenol' (trademark) GH-17s, ex Nippon Gohsei, Japan). The emulsion thus produced was then agitated at a high shear rate (1300 rpm) by a disk impeller for 4 hours at 55°C. At the end of this period, the chloroform had completely evaporated resulting in a dispersion of microspheres whose maximum size was below 14.4 um.

15 Example 2

Preparation of a dispersion of controlled release poly( -hydroxybutyrate- -hydroxy valerate) (PHB/PHV) copolymer microspheres containing sunscreen.

20 6.25 parts of a PHB/PHV copolymer (19% -hydroxy valerate content) and 0.75 parts of a sunscreen were dissolved in 3.68 parts of chloroform. This mixture was then added to a stirred, heated (55°C) 2% w/w aqueous solution of an 25 80% hydrolysed grade of poly (vinyl acetate), a 4% w/w aqueous solution of which has a viscosity of 9.0 cps at 20°C ('Gohsenol' (trademark) OKS-9067K, ex Nippon Gohsei, Japan). The emulsion thus produced was then agitated at 1500 rpm by a disk impeller for 30 3 hours at 55°C. At the end of this period, the chloroform had completely evaporated resulting in a dispersion of microspheres whose maximum size was below 5.0 um.

Examp1 3

Preparation of a dispersion of controlled release EVA copolymer microspheres containing filler.

- 5            6.25 parts of an EVA copolymer (18% vinyl acetate content) and 3.13 parts of "chlorpyrifos" was dissolved in 3.68 parts of chloroform at 55°C. 6.25 parts of surface treated bauxite tailings (average particle size 0.35 um) was dispersed in the
- 10 polymer solution by stirring with magnetic stirrer for 15 min. This mixture was then added to a stirred, heated (55°C) 2% w/w aqueous solution of an 88% hydrolysed grade of poly(vinyl acetate), ('Gohsenol' (trademark) GH-17s, as in Example 1).
- 15 The emulsion thus produced was then agitated at 1500 rpm by a disk impeller at 33°C for 5 hours. At the end of this time, the chloroform had completely evaporated, resulting in a dispersion of microspheres, with the filler encapsulated within
- 20 the microspheres. This was confirmed by a scanning electron microscope investigation.

### CLAIMS

The claims defining the invention are as follows:

1. A method of continuously providing an active ingredient to a place where its presence is desired by means of a controlled release mechanism, the active ingredient being encapsulated in polymer particles which comprise part of an aqueous dispersion of such particles prepared by the steps of

- (a) dissolving in a polymer precursor at least one active ingredient which is completely soluble in the precursor to form a solution;
- (b) stably dispersing the solution in water in the presence of at least one colloid stabilising agent; and
- (c) converting the polymer precursor to polymer and thus forming a dispersion of controlled release microspheres;

the active ingredient being present at a level in excess of the critical blooming concentration and the combination of microsphere size and colloid stabilising agent being such that the dispersion remains stable.

2. A method according to Claim 1 wherein the polymer is selected from the group consisting of ethylene-vinyl acetate copolymers, poly(-hydroxybutyrate -hydroxyvalerate) copolymers, polystyrene, poly(-caprolactone), poly(vinyl pyrrolidone), poly(-hydroxybutyrate) and polylactic and polyglycollic acids and copolymers.



3. A method according to any one of Claims 1 and 2 wherein the active ingredient is selected from the group consisting of a herbicide, an insecticide, and a sunscreen composition.
4. A method according to any one of Claims 1 to 3 wherein the colloid stabilising agent is selected from a highly hydrolysed poly(vinyl acetate) and a nonionic surfactant.
5. A method according to any one of Claims 1 to 4 wherein the polymer precursor is a solution of polymer in a liquid.
6. A method according to Claim 5 wherein the polymer precursor is converted to polymer<sup>microspheres</sup> by evaporation of the liquid.
7. A method according to any one of Claims 1 to 4 wherein the polymer precursor is monomeric in nature.
8. A method according to Claim 7 wherein the monomeric polymer precursor is converted to polymer by addition of an initiator or cross-linking agent.
9. A method according to any one of Claims 1 to 8 wherein the colloid stabilizing agent is present in an amount of from 1 to 5% by weight of the initial emulsion.
10. A method according to any one of Claims 1 to 9 wherein the microspheres produced are from 0.5 to 20  $\mu$ m in size.



11. A method substantially as hereinbefore described with reference to any one of the Examples 1 to 3.

12. A liquid-controlled release composition prepared by the process according to any one of Claims 1 to 11.

13. A liquid controlled-release composition according to claim 12 substantially as hereinbefore described with reference to any one of the Examples 1 to 3.

14. A method of continuously providing an active ingredient using a liquid controlled-release composition prepared by the process according to any one of Claims 1 to 11.

DATED this

21

day of January 1989

*E Ann Hull*

ICI AUSTRALIA OPERATIONS PROPRIETARY LIMITED  
By Its Duly Authorised Officer - E Ann Hull

ABSTRACT

A method of continuously providing an active ingredient to a place where its presence is desired by means of a controlled release mechanism, whereby an active ingredient is encapsulated in a polymer microsphere at a level in excess of the critical "bloomng" composition.

An aqueous dispersion of polymer microspheres containing the active ingredient is formed by a) dissolving the active ingredient(s) in a polymer precursor, b) stably dispersing the solution in water in the presence of at least one colloid stabilising agent and c) converting the polymer precursor to polymer. This dispersion is stable on storage, and there is not much blooming. When the continuous phase is removed, blooming occurs quickly, providing a large initial dose of active ingredient, the rest being released more slowly over time.

The invention is useful for controlled release of substances such as herbicides, insecticides and sunscreens.